

PATENT COOPERATION TREATY

3

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2005/003058

International filing date (day/month/year)
22.03.2005

Priority date (day/month/year)
26.03.2004

International Patent Classification (IPC) or both national classification and IPC
G01N33/483

Applicant
BRACCO IMAGING SPA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☐ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Veronese, A

Telephone No. +49 89 2399-7824



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/003058

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

D1: CALABI LUISELLA ET AL: "Application of high-resolution magic-angle spinning NMR spectroscopy to define the cell uptake of MRI contrast agents." JOURNAL OF MAGNETIC RESONANCE; JUN 2002, vol. 156, no. 2, pages 222-229, XP002288453

D2: CALABI LUISELLA ET AL: "Application of ¹H and ²³Na magic angle spinning NMR spectroscopy to define the HRBC up-taking of MRI contrast agents." JOURNAL OF MAGNETIC RESONANCE (SAN DIEGO, CALIF. : 1997) SEP 2003, vol. 164, no. 1, pages 28-34, XP002288454

NOVELTY

D1 and D2 disclose a method for the *in vitro* determination of the cellular uptake of Dy-DOPTA and other MRI contrast agents (which are also shift reagents) using the Magic Angle Spinning NMR spectroscopy technique (MAS-NMR).

Since the shift reagents used in D1 and D2 are "exogenous substances", the disclosure of D1 and D2 falls into the definition of claim 1-2,4-7,10-14. These claims may therefore not be considered new over the prior art.

Claims 3, 8, 9, which are formulated so that the shift reagent may not be itself the "exogenous substance", are new.

INVENTIVE STEP

D1 and D2 disclose a method for the *in vitro* determination of the cellular uptake of Dy-DOPTA and other MRI contrast agents (which are also shift reagents) using the Magic Angle Spinning NMR spectroscopy technique (MAS-NMR). In D1 and D2 it is the uptake of the shift agent itself which is determined.

The problem underlying claims 3, 8, 9 is the provision of a method to determine the

cellular uptake of certain substances, which are not themselves shift agents (drugs in particular).

As solution, the inventors propose to monitor the NMR signal of the substance to be analysed present inside and outside the cell using the "Magic Angle" NMR technique in the presence of a shift agent.

Since such a method may not be derivable from the prior art, the subject matter of claims 3, 8, 9 is considered also to involve an inventive step.

INDUSTRIAL APPLICATION

The method described in claims 1-14 appears to be industrially applicable.

SECTION VIII

Certain observations on the international application (clarity)

Claim 1 does not explicitly refer to the induction of a LIS in the substance under investigation. Since the method of the invention appears to be based on the induction of a LIS, this claim appears to lack a characterizing feature.